added.

Claims 1, 3-5 and 9-13 are therefore presently pending in the case.

II. Rejection of Claims 1, 3-5 and 9-13 Under 35 U.S.C. § 101

The Action first rejects claims 1, 3-5 and 9-13 under 35 U.S.C. § 101, as allegedly lacking a patentable utility. Applicants respectfully traverse.

As set forth by Applicants in the response filed on October 9, 2003 ("the previous response") to the First Office Action on the merits in this case, which was mailed on June 9, 2003 ("the First Action"), the present invention has a number of substantial and credible utilities, not the least of which is in forensic biology, as described in the specification, at least at page 3, line 21. As described in the specification page 19, lines 3-17, the present sequence defines a number of coding single nucleotide polymorphisms - specifically: a C/G polymorphism at nucleotide position 241 of SEQ ID NOS:1 and 3, which can result in an arginine or glycine at amino acid position 81 of SEQ ID NOS:2 and 4; a C/G polymorphism at nucleotide position 940 of SEQ ID NOS:1 and 3, which can result in a proline or alanine at amino acid position 314 of SEQ ID NOS:2 and 4; a silent C/T polymorphism at nucleotide position 3465 of SEQ ID NOS:1 and 3, both of which result in an aspartate at amino acid position 1155 of SEQ ID NOS:2 and 4; and a silent C/T polymorphism at nucleotide position 5190 of SEQ ID NO:1, both of which result in a glycine at amino acid position 1730 of SEQ ID NO:2. Applicants pointed out that as such polymorphisms are the basis for **forensic** analysis, which is undoubtedly a "real world" utility, the present sequences must in themselves be useful. Thus, the present claims clearly meet the requirements of 35 U.S.C. § 101.

The Examiner questions this assertion of utility, first stating that "the specification fails to provide guidance for using any of the disclosed SNPs to 'distinguish members of a population from one another'" (the Action at page 3). Applicants respectfully point out that the presently described polymorphism can be used to distinguish individual members of the human population from one another in the exact same fashion as any polymorphic marker is so used; specifically, based solely on the **presence** or **absence** of the described polymorphism. Applicants respectfully point out that this is one way in which polymorphic markers such as the presently described polymorphisms have been used for decades in forensic analysis. Therefore, this is clearly a well established technique, and as such, specific guidance does not need to be provided in the present specification, for it has long been established that a patent need not disclose what is well known in the art (*In re Wands*, 8 USPQ 2d

1400 (Fed. Cir. 1988)). Thus, the Examiner's argument does not support the allegation that the presently claimed invention lacks a patentable utility.

Applicants also pointed out in the previous response that in the **worst case** scenario, this polymorphic marker is useful to distinguish 50% of the population (in other words, being present in half of the population). The Examiner correctly cites this exact statement from the previous response ("Applicants argue (page 7, top of the response) that, at worst, each polymorphism is useful to distinguish 50% of the population", the Action at page 3), but then proceeds to **completely** mischaracterize Applicants' argument, stating that "there is no evidence of record that would indicate or even suggest that any of the polymorphisms has a 50% frequency of occurrence" (the Action at page 3). Applicants respectfully point out the **worst case** scenario of a polymorphic marker being present in exactly half of the population is an **inherent feature** of any polymorphic marker. The largest percentage of a population that two polymorphic markers can define is 50% each, and thus this is the least informative marker, *i.e.*, the **worst case** scenario. If one marker is present at a level of less than 50%, then that marker is even **more** informative, *i.e.*, a **greater** percentage of the population can be distinguished on the basis of the marker. Nevertheless, as pointed out by Applicants, the ability to eliminate even 50% of the population from a forensic analysis clearly is a real world, practical utility. Therefore, the Examiner's argument does not support the alleged lack of utility.

The Examiner goes on to state that "unless the polymorphism is *specific* for that subpopulation, there is no way to distinguish a subpopulation from any other population" (the Action at page 3; emphasis in original). In the interest of brevity, Applicants choose not to discuss the numerous flaws in the Examiner's statement, but rather merely point out that Applicants' asserted utility is to distinguish **an individual** from **other individuals**, not "a subpopulation from any other population", and that there are **many** uses of the presently identified polymorphisms in forensic analysis that do **not** involve "distinguish[ing] a subpopulation from any other population". The Examiner next states that "it is unclear as to what useful information can be derived from or how one would interpret a result from genotyping a DNA sample using the claimed polynucleotide to detect the presence or absence of the disclosed polymorphisms", and thus "further experimentation is required to establish a 'real world' use for the claimed polynucleotides" (the Action bridging pages 3 and 4). Applicants hardly know where to begin. Naturally occurring genetic polymorphisms such as those described in the specification as originally filed are both the basis of, and critical to, *inter alia*, forensic genetic analysis intended to resolve issues of, for example, identity or paternity. Forensic analysis based on polymorphisms such

as those identified by Applicants is used to positively identify or rule out suspects in many criminal cases, and in identifying human remains. Paternity determination is based on polymorphisms such as those identified by Applicants to positively identify or rule out individuals suspected of fathering a particular child. Therefore, Applicants find the Examiner's position particularly difficult to comprehend. What could be possibly be more substantial and real world than the loss of an individual's freedom or life through incarceration? What could be possibly be more substantial and real world than the positive identification of human remains? What could be possibly be more substantial and real world than the impact, both economic and emotional, that the results of a paternity analysis has on the individuals directly and indirectly involved? These are all well known and generally accepted uses of polymorphisms such as the polymorphisms identified by Applicants. Without such identified polymorphisms, the skilled artisan would not be able to carry out such forensic or paternal analyses. Thus, the Examiner's argument that the presently described polymorphism is not useful "in currently available form" (the Action at page 4) is also completely without merit. Therefore, the Examiner's arguments with regard to the use of the presently described polymorphism in forensic analysis in no way whatsoever support the allegation that the presently claimed sequence lacks a patentable utility.

Furthermore, Applicants take this opportunity to note that the Examiner repeatedly cites the need for "further experimentation" (the Action at pages 4 (four times), 5 (three times), 7 (three times), 9, 10 and 12), "additional experimentation" (the Action at pages 5, 10 and 11), or the need "to experiment" (the Action at page 8) or " to further investigate" (the Action at page 9), throughout the Action to support the allegation that the present invention lacks a patentable utility. Applicants note for the record that **not once** in the entire Action does the Examiner state the **proper** standard for meeting the requirements of 35 U.S.C. § 101, which is **not** whether "further experimentation" or "additional experimentation" is required to practice certain aspects of the claimed invention, or the need "to experiment" or " to further investigate", but whether **undue** experimentation would be required to practice the claimed invention. The widespread use of polymorphisms such as that described by Applicants in forensic analysis every day **strongly** argues against such a use requiring "undue experimentation". Applicants reiterate that in assessing the question of whether undue experimentation would be required in order to practice the claimed invention, the key term is "undue", not "experimentation". *In re Angstadt and Griffin*, 190 USPQ 214 (CCPA 1976). The need for some experimentation does not render the claimed invention unpatentable. Indeed, a considerable amount of experimentation may be permissible if such experimentation is routinely practiced in the art.

In re Angstadt and Griffin, supra; *Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991). Thus, the Examiner's argument once again does not support the alleged lack of utility, and the present claims clearly meet the requirements of 35 U.S.C. § 101.

In the previous response, Applicants pointed out that the Examiner's argument that "the asserted utilities are not specific to the claimed nucleic acids and are instead general utilities that would be applicable to the broad class of nucleic acids" (the First Action at page 6) is flawed in a number of respects. First, not all nucleic acids contain polymorphic markers. In fact, the basis for forensic analysis is the fact that such polymorphic markers are **not** present in all other nucleic acids, but in fact specific and unique to only a certain subset of the population. Until a polymorphic marker is actually described it cannot be used in forensic analysis. Put another way, simply because there is a likelihood, even a significant likelihood, that a particular nucleic acid sequence will contain a polymorphism and thus be useful in forensic analysis, until such a polymorphism is actually identified and described, such a likelihood is **meaningless**. The Examiner appears to be attempting to use the information presented for the first time by Applicants in the instant specification as hindsight verification that the presently claimed sequence would be expected to have polymorphic markers. Such hindsight analysis based on Applicants discovery is completely improper. Second, the Examiner is clearly confusing the requirement for a **specific** utility, which is the proper standard for utility under 35 U.S.C. § 101, with the requirement for a **unique** utility, which is clearly an improper standard. As clearly set forth by the Federal Circuit in *Carl Zeiss Stiftung v. Renishaw PLC*, 20 USPQ2d 1101 (Fed. Cir. 1991):

> An invention need not be the best or only way to accomplish a certain result, and it need only be useful to some extent and in certain applications: "[T]he fact that an invention has only limited utility and is only operable in certain applications is not grounds for finding a lack of utility." *Envirotech Corp. v. Al George, Inc.*, 221 USPQ 473, 480 (Fed. Cir. 1984)

Following directly from the quote above, an invention does not need to be the **only way** to accomplish a certain result. Thus, the question of whether or not other nucleic acid sequences contain polymorphic markers and can thus be used in forensic analysis is **completely irrelevant** to the present utility inquiry. The **only** relevant question in regard to meeting the standards of 35 U.S.C. § 101 is whether **every** nucleic acid can be so used - and the clear answer to this question is an emphatic **no**. Importantly, the holding in the *Carl Zeiss* case is **mandatory legal authority** that essentially controls the outcome of the present case. This case, and particularly the cited quote, **directly** rebuts the Examiner's argument. Furthermore, the requirement for a unique utility is clearly not the standard adopted by the United States Patent and Trademark Office ("the USPTO"). If every invention were required to have a unique

utility, the USPTO would no longer be issuing patents on batteries, automobile tires, golf balls, golf clubs, and treatments for a variety of human diseases, such as cancer and bacterial or viral infections, just to name a few particular examples, because examples of each of these have already been described and patented. All batteries have the exact same utility - specifically, to provide power. All automobile tires have the exact same utility - specifically, for use on automobiles. All golf balls and golf clubs have the exact same utility - specifically, use in the game of golf. All cancer treatments have the exact same utility - specifically, to treat cancer. All anti-infectious agents have the exact same broader utility - specifically, to treat infections. However, only the briefest perusal of virtually any issue of the Official Gazette provides numerous examples of patents being granted on each of the above compositions every week. Additionally, if a composition needed to be unique to be patented, the entire class and subclass system would be an effort in futility, as the class and subclass system serves solely to group such common inventions, which would not be required if each invention needed to have a unique utility. Thus, the present sequence clearly meets the requirements of 35 U.S.C. § 101.

The Examiner states that "applicants have never been asked to identify a utility that is unique, i.e., not shared by any other compounds or compositions", but "(r)ather, applicants have been required to identify a utility that is specific to the invention claimed, as opposed to one that would apply regardless of the specific properties of the claimed invention" (the Action at page 4; emphasis in original). Applicants will attempt a remedial explanation. The "broad class" to which the Examiner refers is **all** nucleic acids. Applicants reiterate that **not all nucleic acids contain polymorphisms**. Therefore, the question of whether the asserted utilities are "specific to the claimed nucleic acids and are instead general utilities that would be applicable to the broad class of nucleic acids" has **clearly** been laid to rest. The Examiner **repeatedly**, throughout the Action, alleges that he is not requiring "a utility that is unique, i.e., not shared by any other compounds or compositions", but then goes on to **narrowly** define the "broad class" of the invention to include **only** those members that share the asserted utility, and then state that the asserted utilities are "general utilities that would be applicable to the broad class of nucleic acids". Applicants respectfully point out that the "broad class of nucleic acids" **cannot** be redefined to include **only** those nucleic acids that contain polymorphic markers, as the Examiner is forced to do in order to support the allegation that the claimed nucleic acids lack a patentable utility. Alternatively, the Examiner could be attempting to require Applicants to provide a specific technical feature for the present invention, which, while an entirely proper requirement for certain **foreign** patent applications, is **not at all germane** to the question of the utility of the present

United States patent application. Thus, the Examiner's argument is completely improper and in clear defiance of established case law, and therefore is in **no way whatsoever** sufficient to overcome Applicants' assertion of utility. Therefore the present claims are clearly in compliance with 35 U.S.C. § 101.

Thus, as the presently described polymorphism is clearly a part of the family of polymorphisms that have a well established utility, Applicants pointed out in the previous response that the Federal Circuit's holding in *In re Brana,* (34 USPQ2d 1436 (Fed. Cir. 1995), "*Brana*") is directly on point. The Examiner states that "Applicants' arguments (in part) are directed to the utility of the SNPs and not the claimed invention, i.e., the claimed invention is not the disclosed polymorphisms" (the Action at page 5, emphasis in original). Applicants respectfully point out that the described polymorphism is **included** in the claimed nucleic acid sequence, and thus **one** of the utilities of the claimed nucleotide sequence is to use the described polymorphism in forensic analysis, as described in detail, above. Applicants note that the **Examiner himself** continually refers to "genotyping a DNA sample using the **claimed polynucleotide**" (the Action at page 4, twice, emphasis added). Furthermore, Applicants reiterate that only one credible assertion of utility is needed in order to meet the requirements of 35 U.S.C. § 101 (*Raytheon v. Roper*, 220 USPQ 592 (Fed. Cir. 1983); *In re Gottlieb*, 140 USPQ 665 (CCPA 1964); *In re Malachowski*, 189 USPQ 432 (CCPA 1976); *Hoffman v. Klaus*, 9 USPQ2d 1657 (Bd. Pat. App. & Inter. 1988)). The Examiner also repeats the arguments from above that the "instant specification fails to provide sufficient guidance to enable one of skill in the art to use the claimed invention to 'distinguish members of a population from one another'", and that "further experimentation is required to establish a 'real world' use for the claimed polynucleotides for use in forensic analysis" (the Action at page 5) that have been overcome by Applicants, above. Thus, **none** of the Examiner's arguments concerning the use of the described polymorphism in forensic analysis support the alleged lack of utility. Therefore, the present claims clearly meet all standards for patentability under 35 U.S.C. § 101.

As set forth in the previous response, Applicants point out that it has been clearly established that a statement of utility in a specification must be accepted absent reasons why one skilled in the art would have reason to doubt the objective truth of such statement. *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA, 1974; "*Langer*"); *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA, 1971). As clearly set forth in *Langer*:

> As a matter of Patent Office practice, a specification which contains a disclosure of utility which corresponds in scope to the subject matter sought to be patented must be

> taken as sufficient to satisfy the utility requirement of § 101 for the entire claimed subject matter unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope.

Langer at 297, emphasis in original. As set forth in the MPEP, "Office personnel must provide **evidence** sufficient to show that the statement of asserted utility would be considered 'false' by a person of ordinary skill in the art" (MPEP, Eighth Edition at 2100-40, emphasis added). The Examiner attempts to discount the holding in *Langer*, implying that *Langer* "appear(s) to address the issue of credibility of an asserted utility", but that "(i)n this case, the rejection is based on the specification's failure to disclose a specific and substantial asserted utility" (the Action at page 6). This **complete mischaracterization** of the holding from *Langer* is laid to rest by examining the actual words of *Langer*; namely, the reference to "the utility requirement of § 101". Applicants note for the record that *Langer* does not say "the credibility issue of the utility requirement of § 101", but, rather, **the** utility requirement of § 101. In other words, unless the Examiner can provide **evidence** that the polymorphism described by Applicants can **not** be used in forensic analysis, Applicants' assertion of utility as set forth in the specification as originally filed "must be taken as sufficient to satisfy the utility requirement of § 101". Absent such **evidence** from the Examiner, or case law authority overturning the holding in *Langer*, as the skilled artisan would readily understand that the present polymorphic marker has utility in forensic analysis, the present claims clearly meet the requirements of 35 U.S.C. § 101.

The Examiner next states that "applicants' assertion that the claimed sequence is a human Ten-m4 protein variant is acknowledged", but then incredulously states that "there is no assertion that the proteins of SEQ ID NO:2 and 4 have Ten-m4/cdz protein activity" (the Action at page 6). This tortured logic borders on the absurd. The Examiner attempts to justify this position by stating that "(i)nstead, the specification indicates that SEQ ID NO:2 and 4 'share structural similarity' with proteins that appear to have distinct biological activities - 1) murine Ten-m4/cdz and 2) proteins identified as gamma-heregulins" (the Action at page 6). Applicants respectfully point out that the **fact** that SEQ ID NO:2 and SEQ ID NO:4 share structural similarity with both Ten-m4/cdz proteins and gamma-heregulins does **not** mean that Applicants have not asserted that the presently claimed sequences have Ten-m4/cdz activity. Applicants note for the record that the title of the application as originally filed is "Novel Human TEN-M4/cdz Proteins and Polynucleotides Encoding the Same", **not** "Novel Human Gamma-Heregulin Proteins and Polynucleotides Encoding the Same", thus clearly establishing that the presently claimed sequences, while having structural similarity to gamma-heregulins,

are asserted by Applicants to have Ten-m4/cdz activity. Therefore, as Applicants have **clearly** asserted that the presently claimed sequence encodes a human Ten-m4/cdz protein, the Examiner's arguments are **completely** without merit.

The Examiner next states that "(o)ne of skill in the art recognizes that only by empirical characterization can the function of a protein be ascertained" (the Action at page 7). The Examiner seems to be requiring an example in the specification as originally filed demonstrating that the presently claimed sequence has Ten-m4/cdz activity. However, this position as applied to the presently claimed sequences is **completely** inconsistent with mandatory legal precedent, the knowledge of those of skill in the art, as well as the policy of the USPTO. With regard to mandatory legal precedent, it has long been established that "there is no statutory requirement for the disclosure of a specific example" (*In re Gay*, 309 F.2d 769, 135 USPQ 311 (CCPA, 1962)). With regard to the knowledge of those of skill in the art, as opposed to the two articles cited by the Examiner in the First Action (Brenner, *Trends Genet.* **15**:132-133, 1999, and Scott *et al.*, *Nat. Genet.* **21**:440-443, 1999) that call into doubt prediction of protein function from homology information and the usefulness of bioinformatic predictions, Applicants submit that the **overwhelming majority** of those of skill in the relevant art believe bioinformatic prediction to be a powerful and useful tool, as evidenced by hundreds if not thousands of journal articles, for example Bateman *et al.*, *Nucl. Acids Res.* **30**:276-280, 2002, Mulder *et al.*, *Nucl. Acids Res.* **31**:315-318, 2003, Wu *et al.*, *Nucl. Acids Res.* **30**:35-37, 2002, and Letunic *et al.*, *Nucl. Acids Res.* **30**:242-244, 2002 (abstracts provided in **Exhibit A**), which describe Pfam, InterPro, PIR and SMART, respectively, four of the most widely used bioinformatic prediction programs, and would thus believe that Applicants sequence is a Ten-m4/cdz protein, which is the standard for meeting the utility requirement of 35 U.S.C. § 101. With regard to the policy of the USPTO, Example 10 of the Revised Interim Utility Guidelines Training Materials (pages 53-55; **Exhibit B**), clearly establishes that a rejection under 35 U.S.C. § 101 as allegedly lacking a patentable utility and under 35 U.S.C. § 112, first paragraph as allegedly unusable by the skilled artisan due to the alleged lack of patentable utility, is not proper when a full length sequence has a similarity score greater than 95% to a protein having a known function. Therefore, the USPTO's **own** examination guidelines clearly indicate that "empirical characterization" is **not required** before "the function of a protein be ascertained". Thus, the Examiner's argument is completely improper, and therefore is in **no way whatsoever** sufficient to overcome Applicants' assertion of utility. Therefore the present claims are clearly in compliance with 35 U.S.C. § 101.

The Examiner next states that "even if SEQ ID NO:2 and 4 have Ten-m4/cdz 'activity', the prior art does not define such activity" (the Action bridging pages 7 and 8). Applicants respectfully point out that the role of Ten-m4/cdz proteins in development has been well-known to those of skill in the art for a number of years. In 1997, Levine *et al.* (*Gene* **200**:59-74, "Levine"; abstract provided in **Exhibit C**) generated a null allele of the Drosophila odz gene, and clearly established that "(t)he true null phenotype of odz in segmentation is now seen to be very similar to that originally characterized, with each odd segment removed" (Levine, abstract). Additionally, Ben-Zur *et al.* (*Dev. Biol.* **217**:107-120, 2000, "Ben-Zur"; abstract provided in **Exhibit D**) state that "(t)he Drosophila pair-rule gene odz (Tenm) has many patterning roles throughout development" (Ben-Zur, abstract). Therefore, as the prior art has clearly established the role of Ten-m4/cdz proteins in development, the Examiner's argument is without merit, and does not serve to support the allegation that the presently claimed sequences lack a patentable utility.

Additionally, in the previous response, Applicants provided a publication by Feng *et al.* (*J. Biol. Chem.* **277**:26128-26135, 2002) that details the role of Ten-m4/cdz proteins in development. The Examiner states that "the reference of Feng et al. was not available at the time of filing of the instant application" (the Action at page 8). Applicants respectfully point out that this fact is **completely and totally irrelevant** with regard to the **utility** issue at hand. Applicants pointed to the Feng *et al.* reference, **not** to evidence that the role of Ten-m4/cdz proteins in development was known in the art at the time the present application was filed (which was clearly established by other investigators, see **Exhibit C** and **Exhibit D**), but, rather, to evidence that other skilled artisans have **confirmed** Applicants' assertion that the presently claimed Ten-m4/cdz sequence has a role in development. Thus, this argument by the Examiner also in no way supports the alleged lack of utility.

The Examiner next states that "based on the vague characterization of Ten-m4/cdz as a stress response protein (Wang et al. and Oohashi et al.), one of skill in the art would not recognize the biological significance of the claimed sequences" (the Action at page 7). Given the well established role of Ten-m4/cdz proteins in development (see **Exhibit C** and **Exhibit D**), Applicants submit that those of skill in the art would readily understand the "biological significance" of the presently claimed sequence - specifically, it's involvement in development. Thus, the Examiner's argument hardly serves to overcome Applicants' assertion of utility. Absent **evidence** from the Examiner that those of skill in the art would not recognize the "biological significance" of Ten-m4/cdz proteins in developmental processes, the presently claimed sequence clearly meets the requirements of 35 U.S.C. § 101.

Therefore, as pointed out by Applicants in the previous response, given the known involvement of Ten-m4/cdz proteins in development, as just one example of the utility of the present nucleotide sequences, the skilled artisan would readily appreciate the utility of tracking expression of the presently claimed sequence. The specification details, at least at page 6, lines 24-27, that the present nucleotide sequences have utility in assessing gene expression patterns using high-throughput DNA chips. Such "DNA chips" clearly have utility, as evidenced by hundreds of issued U.S. Patents, as exemplified by U.S. Patent Nos. 5,445,934, 5,556,752, 5,744,305, 5,837,832, 6,156,501 and 6,261,776 (**Exhibits E-J**; copies of issued U.S. Patents not provided pursuant to requests from the USPTO). As the present sequences are specific markers of human chromosome 11 (see below), and such specific markers are targets for the discovery of drugs that are associated with human disease, those of skill in the art would instantly recognize that the present nucleotide sequences would be an ideal, novel candidate for assessing gene expression using such DNA chips. Given the widespread utility of such "gene chip" methods using *public domain* gene sequence information, there can be little doubt that the use of the presently described *novel* sequences involved in development would have great utility in such DNA chip applications. Clearly, compositions that enhance the utility of such DNA chips, such as the presently claimed nucleotide sequences, must in themselves be useful.

Further evidence of the "real world" substantial utility of the present invention is further provided by the fact that there is an entire industry established based on the use of gene sequences or fragments thereof in a gene chip format. Perhaps the most notable gene chip company is Affymetrix. However, there are many companies which have, at one time or another, concentrated on the use of gene sequences or fragments, in gene chip and non-gene chip formats, for example: Gene Logic, ABI-Perkin-Elmer, HySeq and Incyte. In addition, one such company (Rosetta Inpharmatics) was viewed to have such "real world" value that it was acquired by large a pharmaceutical company (Merck) for significant sums of money (net equity value of the transaction was $620 million). The "real world" substantial industrial utility of gene sequences or fragments would, therefore, appear to be widespread and well established. Clearly, persons of skill in the art, as well as venture capitalists and investors, readily recognize the utility, both scientific and commercial, of genomic data in general, and specifically human genomic data. Billions of dollars have been invested in the human genome project, resulting in useful genomic data (see, *e.g.*, Venter *et al.*, *Science* **291**:1304, 2001; **Exhibit K**). The results have been a stunning success as the utility of human genomic data has been widely recognized as a great gift to humanity (see, *e.g.*, Jasny and Kennedy, *Science* **291**:1153, 2001; **Exhibit L**).

Clearly, the usefulness of human genomic data, such as the presently claimed nucleic acid molecules, is substantial and credible (worthy of billions of dollars and the creation of numerous companies focused on such information) and well-established (the utility of human genomic information has been clearly understood for many years). Thus, the present sequence clearly meets the requirements of 35 U.S.C. § 101.

The Examiner questions this assertion of utility, stating that "the reference of Oohashi et al. states that it is not clear as to the biological activity of Ten-m4", and "(t)hus, one of ordinary skill in the art would not recognize the so-called 'well-established' role of ten-m proteins in development" (the Action at page 8). Applicants respectfully point out that the lack of 100% consensus on the role of Ten-m4/cdz proteins in development is **completely irrelevant** to the question of whether the claimed nucleic acid sequence has a substantial and specific utility. Applicants respectfully point out that the legal test for utility simply involves an assessment of whether those skilled in the art would find any of the utilities described for the invention to be **believable**. Applicants submit that given the publications by Levine *et al.*, Ben-Zur *et al.* (see **Exhibit C** and **Exhibit D**), and Feng *et al.* (see **Exhibit E** from the previous response), those of skill in the art would **believe** that Ten-m4/cdz proteins have a role in development. As **believability** is the standard for meeting the utility requirement of 35 U.S.C. § 101, and **not** 100% consensus, Applicants submit that the present claims must clearly meet the requirements of 35 U.S.C. § 101.

The Examiner further questions this utility, stating that "any sequence can be included as a component of a gene chip" (the Action at page 8). As pointed out by Applicants in the previous response, this argument is flawed in **at least** three respects. First, the asserted utility is in assessing **gene expression patterns** using high-throughput DNA chips. Applicants reiterate that only expressed sequences can be used to track gene expression, not just any nucleic acid. Second, Applicants point out that the presently claimed sequence is involved in development, which clearly distinguishes the claimed sequence from "any sequence". Expression profiling does not even require a knowledge of the function of the particular nucleic acid on the chip - rather the gene chip indicates which DNA fragments are expressed at greater or lesser levels in two or more particular tissue types. Applicants point out that skilled artisans already have used and continue to use sequences such as Applicants in gene chip applications without further experimentation, which directly rebuts the Examiner's allegation that the skilled artisan "would not be able to use the claimed invention in currently available form" (the Action at page 7). Third, the Examiner is still clearly confusing the requirements

of a **specific** utility, which is the **proper** standard for utility under 35 U.S.C. § 101, with the requirement for a **unique** utility, which is clearly an **improper** standard (*Carl Zeiss Stiftung v. Renishaw PLC, supra*). Once again, the question of whether or not **other** nucleic acid sequences can be used to assess gene expression patterns using DNA chips is **completely irrelevant** to the present utility inquiry. The **only** relevant question in regard to meeting the standards of 35 U.S.C. § 101 is whether **every** nucleic acid can be so used - and the clear answer to this question is an emphatic **no**. Applicants respectfully point out that Examiner is once again attempting to redefine "any sequence" to include **only** those nucleic acids that are expressed and involved in development in order to support the allegation that the claimed nucleic acids lack a patentable utility, which is improper under the law as well as the policy of the USPTO. Thus, the present claims clearly meet the requirements of 35 U.S.C. § 101.

The Examiner further questions this asserted utility, stating that "any information derived from gene expression analysis using the claimed sequences would be meaningless as the specification fails to provide guidance for interpreting any result obtained thereby" (the Action at page 8). Applicants respectfully submit that the skilled artisan would readily understand the meaning of the results "derived from gene expression analysis using the claimed sequences". For example, if the claimed sequence was found to be expressed at higher levels in certain developmental stages, given the well-established role of Ten-m4/cdz proteins in development, the skilled artisan would immediately understand that the presently claimed sequence has a direct role in the development of tissues associated with that particular developmental stage. The fact that there is an **entire, multimillion dollar industry** established based on the use of gene sequences or fragments thereof in a gene chip format, supports Applicants' position that those of skill in the art do not need "guidance for interpreting any result obtained thereby". Applicants once again point out that, as a matter of law, it is well settled that a patent need not disclose what is well known in the art (*In re Wands, supra*). Thus, the Examiner's argument once again does not support the alleged lack of utility, and the present claims clearly meet the requirements of 35 U.S.C. § 101.

The Examiner then erroneously states that "(e)vidence of commercial success, while sometimes persuasive as secondary evidence of non-obviousness, is immaterial to utility and enablement" (the Action at page 9). This statement could not be **further** from the truth. The Examiner repeatedly alleges that the presently claimed invention does not have a "real world" use (the Action at least at pages 4 (twice), 5, 7, and 12), and that the presently claimed invention is not useful "in currently

available form" (the Action at least at pages 4, 5, 7, 10, 11 and 12). The evidence of commercial success **directly** rebuts the Examiner's allegation that the presently claimed sequences do not have a "real world" context of use and is not useful "in currently available form", unless it is the position of the Examiner that the entire gene chip industry does not exist in the "real world". Thus, "applicants' own statement regarding the widespread use of such gene chips using public domain gene sequences" (the Action at page 8) is **not**, as **completely mischaracterized** by the Examiner, evidence that "any sequence can be included as a component of a gene chip" (the Action at page 8), but, rather, **direct** evidence that the presently claimed sequence is in fact useful "in currently available form". Therefore, the Examiner's argument is **completely** without merit, and in **no way** supports the allegation that the presently claimed invention lacks a patentable utility.

Next, the Examiner states that "*(a)ny* expressed or non-expressed sequence can be used for gene expression monitoring" (the Action at page 9, emphasis in original). Once again, Applicants hardly know where to begin. It is completely beyond all bounds of logic that "*any* ... non-expressed sequence can be used for gene expression monitoring". **By definition**, non-expressed sequences are **not expressed**, and thus **cannot** be used to monitor gene **expression**. The Examiner is requested to provide **evidence** that "*any* ... non-expressed sequence can be used for gene expression monitoring", in order to support this position. Absent such **evidence**, the Examiner's argument is **completely** without merit, and in **no way** supports the allegation that the presently claimed invention lacks a patentable utility.

As set forth in the previous response, as yet a further example of the utility of the presently claimed polynucleotide, as described in the specification at least at page 3, lines 12-15, the present nucleotide sequence has a specific utility in "identification of coding sequence" and "mapping a unique gene to a particular chromosome". As described in the specification as originally filed at page 18, lines 30-32, the gene encoding the presently claimed sequences was likely present on human chromosome 11, based on homology to GenBank Accession Number AP002515. In fact, alignment of the presently claimed sequences with GenBank accession number AP002515, in addition to GenBank accession numbers AP002768 and AP002957 (three overlapping clones from human chromosome 11) shows that the human gene corresponding to the presently claimed sequence is dispersed on 28 exons of human chromosome 11 (alignments and first pages of GenBank reports are presented in **Exhibit M**). Applicants reiterate that only a minor percentage (2-4%) of the genome actually encodes exons, which in-turn encode amino acid sequences. Equally significant is that the

claimed polynucleotide sequence defines how the encoded exons are actually spliced together to produce an active transcript (*i.e.*, the described sequences are useful for functionally defining exon splice-junctions). It is well-known that exon splice junctions can often be hot spots for erroneous events leading to cancer. As described in the specification as originally filed at page 3, lines 15-18, the claimed sequences "identify biologically verified exon splice junctions, as opposed to splice junctions that may have been bioinformatically predicted from genomic sequence alone". The specification also details that "sequences derived from regions adjacent to the intron/exon boundaries of the human gene can be used to design primers for use in amplification assays to detect mutations within the exons, introns, splice sites (*e.g.*, splice acceptor and/or donor sites), *etc.*, that can be used in diagnostics and pharmacogenomics" (specification at page 12, lines 22-27). Applicants respectfully submit that the practical scientific value of biologically validated, expressed, spliced, and polyadenylated mRNA sequences is readily apparent to those skilled in the relevant biological and biochemical arts. Thus, the present sequence clearly meets the requirements of 35 U.S.C. § 101.

Clearly, the present polynucleotide provides exquisite specificity in localizing the specific region of human chromosome 11 that contains the gene encoding the given polynucleotide, a utility not shared by virtually any other nucleic acid sequences. In fact, it is this specificity that makes this particular sequence so useful. Early gene mapping techniques relied on methods such as Giemsa staining to identify regions of chromosomes. However, such techniques produced genetic maps with a resolution of only 5 to 10 megabases, far too low to be of much help in identifying specific genes involved in disease. The skilled artisan readily appreciates the significant benefit afforded by markers that map a specific locus of the human genome, such as the present nucleic acid sequence. For further evidence in support of the Applicants' position, the Examiner is requested to review, for example, section 3 of Venter *et al.* (*supra*, at pp. 1317-1321, including Fig. 11 at pp.1324-1325; see **Exhibit K**), which demonstrates the significance of expressed sequence information in the structural analysis of genomic data. The presently claimed polynucleotide sequence defines a biologically validated sequence that provides a unique and specific resource for mapping the genome essentially as described in the Venter *et al.* article. Thus, the present claims clearly meet the requirements of 35 U.S.C. § 101.

The Examiner once again questions this utility, stating that "it is noted that, at the time of filing of the instant application, there was no evidence or record or line of reasoning to suggest that the claimed sequences were useful for identifying any specific region of chromosome 11 or that the region comprising the claimed sequences was shared by virtually any other nucleic acids" (the Action at

page 10). The first part of the Examiner's argument is clearly refuted by simple examination of the specification as originally filed, as detailed above, which clearly indicated that the gene encoding the presently claimed sequences was likely present on human chromosome 11, based on homology to GenBank Accession Number AP002515, and that, "(a)s such, the described sequences can also be used to map the corresponding coding regions of the human genome" (specification from page 18, line 32 to page 19, line 2). Thus, clearly, "at the time of filing of the instant application", there was in fact "evidence or record or line of reasoning to suggest that the claimed sequences were useful for identifying any specific region of chromosome 11", specifically, the region of human chromosome 11 defined by GenBank Accession Number AP002515. As to evidence "that the region comprising the claimed sequences was shared by virtually any other nucleic acids", Applicants respectfully reiterate that this specific region of human chromosome 11 is shared by virtually **no** other nucleic acids, **not** "any other nucleic acids". Further, Applicants respectfully point out that it is well established that the skilled artisan would understand that a **unique** human sequence (Applicants point to the lack of any prior art rejection in the Action) would share a chromosomal location with virtually **no** other nucleic acids. Thus, the Examiner's argument in no way whatsoever supports the alleged lack of utility.

The Action further questions this utility, once again stating that "*any* human polynucleotide which (*sic*) encodes a protein can be used to determine the specific chromosome which (*sic*) contains that locus" (the Action at page 10). Applicants submit that the Examiner is once again confusing the requirements of a **specific** utility, which is the proper standard for utility under 35 U.S.C. § 101, with the requirement for a **unique** utility, which is clearly an **improper** standard (*Carl Zeiss Stiftung v. Renishaw PLC, supra*). The fact that a small number of other nucleotide sequences could be used to map the protein coding regions in this specific region of chromosome 11 does not mean that the use of Applicants' sequence to map the protein coding regions of chromosome 11 is not a specific utility. Applicants reiterate that the question of whether or not **other** nucleic acid sequences "can be used to determine the specific chromosome which (*sic*) contains that locus" is **completely irrelevant** to the present utility inquiry. The **only** relevant question in regard to meeting the standards of 35 U.S.C. § 101 is whether **every** nucleic acid can be so used - and the clear answer to this question is once again an emphatic **no**. Applicants respectfully point out that in this case the Examiner is attempting to narrow the broad class of "*any* human polynucleotide" to include **only** "any human polynucleotide which (*sic*) encodes a protein" in order to support the allegation that the claimed nucleic acids lack a patentable utility, which Applicants point out once again is improper under the law as well

as the policy of the USPTO. Thus, the present claims clearly meet the requirements of 35 U.S.C. § 101.

Rather, Applicants pointed out in the previous response that, as set forth by the Federal Circuit, "(t)he threshold of utility is not high: An invention is 'useful' under section 101 if it is capable of providing some identifiable benefit." *Juicy Whip Inc. v. Orange Bang Inc.*, 51 USPQ2d 1700 (Fed. Cir. 1999) (citing *Brenner v. Manson*, 383 U.S. 519, 534 (1966)). Additionally, the Federal Circuit has stated that "(t)o violate § 101 the claimed device must be totally incapable of achieving a useful result." *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 (Fed. Cir. 1992), emphasis added. *Cross v. Iizuka* (224 USPQ 739 (Fed. Cir. 1985); "*Cross*") states "any utility of the claimed compounds is sufficient to satisfy 35 U.S.C. § 101". *Cross* at 748, emphasis added. Indeed, the Federal Circuit recently emphatically confirmed that "anything under the sun that is made by man" is patentable (*State Street Bank & Trust Co. v. Signature Financial Group Inc.*, 47 USPQ2d 1596, 1600 (Fed. Cir. 1998), citing the U.S. Supreme Court's decision in *Diamond vs. Chakrabarty*, 206 USPQ 193 (S.Ct. 1980)).

The Examiner seems to discount the case law cited by Applicants, stating "(i)n *Juicy Whip Inc. v. Orange Bang Inc.*, the issue of utility was discussed in regard to a juice dispenser, in *Brooktree Corp. v. Advanced Micro Devices, Inc.*, the issue of utility was discussed in regard to digital analog conversion circuitry, and in *State Street Bank & Trust Co. v. Signature Financial Group Inc.*, the issue of utility was discussed in regard to a business method" (the Action bridging pages 11 and 12). Applicants respectfully point out that the holding in each of these cases is **mandatory legal authority**, and that the Examiner **must** follow the precedent as applied to the broad issue at hand in each cited case, unless a case is specifically limited to it's facts by the **Court itself**. Furthermore, Section 101 of the Patent Act of 1952, 35 U.S.C. § 101, provides that "[w]hoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof," may obtain a patent on the invention or discovery. Applicants point out that 35 U.S.C. § 101 covers devices (machines) as well as compositions, and makes no distinction between the two with regard to meeting the burden of complying with 35 U.S.C. § 101. Additionally, *Juicy Whip Inc. v. Orange Bang Inc.* cites *Brenner v. Manson*, 383 U.S. 519 (1966), which the Examiner obviously believes is relevant to the present case, since the Examiner himself cited this exact case in the First Action (the First Action at page 8). Also, *Diamond vs. Chakrabarty, supra*, specifically concern compositions. Thus, this argument is completely improper, and totally fails to support the alleged lack

of utility of the presently claimed compositions.

The Examiner then states that "in contrast to *Cross v. Iizuka*, the claimed invention fails to benefit the public in currently available form" (the Action at page 12). However, as discussed at length, above, the ability to use the polymorphisms described by Applicants in forensic analysis, and the widespread use of nucleotide sequences such as Applicants in numerous applications, from assessing gene expression patterns using gene chips to mapping the protein coding regions of chromosomes, is direct evidence that the claimed invention in fact does "benefit the public in currently available form". Therefore, the Examiner's argument is **completely** without merit, ans in **no way** supports the allegation that the presently claimed invention lacks a patentable utility.

Finally, Applicants pointed out in the previous response that the requirements set forth in the Action for compliance with 35 U.S.C. § 101 do not comply with the requirements set forth by the USPTO itself for compliance with 35 U.S.C. § 101. While Applicants are well aware of the new Utility Guidelines set forth by the USPTO, Applicants respectfully point out that the current rules and regulations regarding the examination of patent applications is and always has been the patent laws as set forth in 35 U.S.C. and the patent rules as set forth in 37 C.F.R., not the Manual of Patent Examination Procedure or particular guidelines for patent examination set forth by the USPTO. Furthermore, it is the job of the judiciary, not the USPTO, to interpret these laws and rules. Applicants are unaware of any significant recent changes in either 35 U.S.C. § 101, or in the interpretation of 35 U.S.C. § 101 by the Supreme Court or the Federal Circuit that is in keeping with the new Utility Guidelines set forth by the USPTO. This is underscored by numerous patents that have been issued over the years that claim nucleic acid fragments that do not comply with the new Utility Guidelines. As examples of such issued U.S. Patents, the Examiner is invited to review U.S. Patent Nos. 5,817,479, 5,654,173, and 5,552,281 (each of which claims short polynucleotides; **Exhibits N-P**; copies of issued U.S. Patents not provided pursuant requests from the USPTO), and recently issued U.S. Patent No. 6,340,583 (which includes no working examples; **Exhibit Q**; copies of issued U.S. Patents not provided pursuant to requests from the USPTO), none of which contain examples of the "real-world" utilities that the Examiner seems to be requiring. As issued U.S. Patents are presumed to meet all of the requirements for patentability, including 35 U.S.C. §§ 101 and 112, first paragraph (see Section III, below), Applicants submit that the present polynucleotides must also meet the requirements of 35 U.S.C. § 101. While Applicants understand that each application is examined on its own merits, Applicants are unaware of any changes to 35 U.S.C. § 101, or in the interpretation of

35 U.S.C. § 101 by the Supreme Court or the Federal Circuit, since the issuance of these patents that render the subject matter claimed in these patents, which is similar to the subject matter in question in the present application, as suddenly non-statutory or failing to meet the requirements of 35 U.S.C. § 101. Thus, holding Applicants to a different standard of utility would be arbitrary and capricious, and, like other clear violations of due process, cannot stand.

The Examiner states that "the guidelines were promulgated by the PTO in accordance with all applicable case law and thus are believed to be consistent therewith" (the Final Action at page 12). Unfortunately, as discussed at length above, this is simply **not true**. Applicants have noted numerous cases that directly contradict the USPTO's new utility guidelines, and are unaware of any Federal Circuit or Supreme Court decisions to date that have examined, let alone validated, the current utility guidelines. And while Applicants understand that the USPTO is bound to follow their own guidelines, until a definitive ruling by the Federal Circuit or the Supreme Court, these guidelines should not be confused in **any way** with the force of law. There are numerous examples over the years of USPTO guidelines that have been found not to comport with the patent laws and rules. As just **one** example of the Federal Circuit overturning guidelines enacted *sua sponte* by the USPTO, the Examiner is invited to review *In re Brana, supra*. Thus, this argument also fails to support the alleged lack of utility.

For each of the foregoing reasons, as well as the reasons set forth in the previous response, which are incorporated herein in their entirety by reference, Applicants submit that as the presently claimed nucleic acid molecules have been shown to have a substantial, specific, credible and well-established utility, the rejection of claims 1, 3-5 and 9-13 under 35 U.S.C. § 101 has been overcome, and request that the rejection be withdrawn.

III. Rejection of Claims 1, 3-5 and 9-13 Under 35 U.S.C. § 112, First Paragraph

The Action next rejects claims 1, 3-5 and 9-13 under 35 U.S.C. § 112, first paragraph, since allegedly one skilled in the art would not know how to use the invention, as the invention allegedly is not supported by a specific, substantial, and credible utility or a well-established utility. Applicants respectfully traverse.

Applicants submit that as claims 1, 3-5 and 9-13 have been shown to have "a specific, substantial, and credible utility", as detailed in section II above, the present rejection of claims 1, 3-5 and 9-13 under 35 U.S.C. § 112, first paragraph, cannot stand.

Applicants therefore request that the rejection of claims 1, 3-5 and 9-13 under

35 U.S.C. § 112, first paragraph, be withdrawn.

IV. Rejection of Claim 4 Under 35 U.S.C. § 112, First Paragraph

The Action next rejects claim 4 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Applicants respectfully traverse.

As pointed out by Applicants in the previous response, 35 U.S.C. § 112, first paragraph, requires that the specification contain a written description of the invention. The Federal Circuit in *Vas-Cath Inc. v. Mahurkar* (19 USPQ2d 1111 (Fed. Cir. 1991); "*Vas-Cath*") held that an "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.*" *Vas-Cath*, at 1117, emphasis in original. However, it is important to note that the above finding uses the terms reasonable clarity to those skilled in the art. Further, the Federal Circuit in *In re Gosteli* (10 USPQ2d 1614 (Fed. Cir. 1989); "*Gosteli*") held:

> Although [the applicant] does not have to describe exactly the subject matter claimed, ... the description must clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed.

Gosteli at 1618, emphasis added. Additionally, *Utter v. Hiraga* (6 USPQ2d 1709 (Fed. Cir. 1988); "*Utter*"), held "(a) specification may, within the meaning of 35 U.S.C. § 112 ¶1, contain a written description of a broadly claimed invention without describing all species that claim encompasses" (*Utter*, at 1714). Therefore, all Applicants must do to comply with 35 U.S.C. § 112, first paragraph, is to convey the invention with reasonable clarity to the skilled artisan.

Further, the Federal Circuit has held that an adequate description of a chemical genus "requires a precise definition, such as by structure, formula, chemical name or physical properties" sufficient to distinguish the genus from other materials. *Fiers v. Sugano*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993; "*Fiers*"). *Fiers* goes on to hold that the "application satisfies the written description requirement since it sets forth the ... nucleotide sequence" (*Fiers* at 1607). In other words, provision of a structure and formula - the nucleotide sequence - renders the application in compliance with 35 U.S.C. § 112, first paragraph.

More recently, the standard for complying with the written description requirement in claims involving chemical materials has been explicitly set forth by the Federal Circuit:

In claims involving chemical materials, generic formulae usually indicate with specificity

> what the generic claims encompass. One skilled in the art can distinguish such a formula from others and can identify many of the species that the claims encompass. Accordingly, such a formula is normally an adequate description of the claimed genus. *Regents of Univ. of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

Thus, a claim describing a genus of nucleic acids by structure, formula, chemical name or physical properties sufficient to allow one of ordinary skill in the art to distinguish the genus from other materials meets the written description requirement of 35 U.S.C. § 112, first paragraph. As further elaborated by the Federal Circuit in *Regents of Univ. of California v. Eli Lilly and Co.*:

> In claims to genetic material ... a generic statement such as 'vertebrate insulin cDNA' or 'mammalian insulin cDNA', without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art cannot, as one can do with a fully described genus, visualize or recognize the identity of members of the genus. (Emphasis added)

Thus, as opposed to the situation set forth in *Regents of Univ. of California v. Eli Lilly and Co.* and *Fiers*, the nucleic acid sequences of the present invention are not distinguished on the basis of function, or a method of isolation, but in fact are distinguished by structural features - a chemical formula, *i.e.*, the *sequence itself.*

Thus, Applicants pointed out that using the nucleic acid and amino acid sequences of the present invention (as set forth in the Sequence Listing), the skilled artisan would readily be able to **distinguish** the claimed nucleic acids from other materials on the basis of the specific structural description provided. Polynucleotides that encode SEQ ID NO:4 are within the genus of the instant claims, while those that lack this **structural** feature lie outside the genus. Claim 4 thus meets the written description requirement.

The Examiner states that "the single disclosed representative species of SEQ ID NO:3 fails to adequately describe the claimed invention" (the Action at page 14). Applicants note for the record that since SEQ ID NO:4 is a fragment of SEQ ID NO:2, as acknowledged by the Examiner, that there are a large number of representative species disclosed in the specification as originally filed that adequately describes "an isolated nucleic acid molecule comprising a nucleotide sequence encoding the amino acid sequence shown in SEQ ID NO:4". As just **one** additional example, SEQ ID NO:1 is "a nucleotide sequence encoding the amino acid sequence shown in SEQ ID NO:4". Is it the position of the Examiner that SEQ ID NO:1 is not disclosed in the specification as originally filed? Furthermore, as

any fragment of SEQ ID NO:1 that contains more than the first 4875 nucleotides of SEQ ID NO:1 is "a nucleotide sequence encoding the amino acid sequence shown in SEQ ID NO:4", the specification as originally filed describes **thousands** of "isolated nucleic acid molecule[s] comprising a nucleotide sequence encoding the amino acid sequence shown in SEQ ID NO:4". Thus, the Examiner's argument does not support the allegation that claim 4 lacks sufficient written description.

Applicants noted for the record in the previous response that the Examiner's comments concerning the scope of claims 1 and 4, as set forth on page 10 of the First Action, are not only directly in contrast with the relevant case law concerning the requirements under 35 U.S.C. § 112, first paragraph, as set forth in detail above, but are also contradicted by the wealth of case law concerning claim scope. The Examiner "requests that applicants provide supporting details of how the examiner's comments are 'directly in contrast with the relevant case law', 'are contradicted by the wealth of case law concerning claim scope', and are 'erroneous'" (the Action at page 15). Applicants will attempt a remedial explanation. Claim 1 and claim 4 both use the term "(a)n isolated nucleic acid molecule **comprising**" (emphasis added). Hundreds of years of case law have clearly established that the term "comprising" means that additional elements other than those specifically recited in the claim are encompassed within the scope of the claim. Furthermore, a large number of such additional elements are described in the specification as originally filed, including, but not limited to, promoter elements and selectable markers. Therefore, the Examiner's assertion that "any variation within the genus of nucleic acids of claim 1 would arise due to the addition of elements that are not part of the inventor's particular contribution" (the First Action at page 10) is **completely and totally false**. Applicants therefore once again assert for the record that the scope of claims 1 and 4 are not limited in **any way** by the Examiner's erroneous comments, and should be given their fullest possible scope.

For each of the foregoing reasons, Applicants submit that the rejection of claim 4 under 35 U.S.C. § 112, first paragraph, has been overcome, and request that the rejection be withdrawn.

V. Conclusion

The present document is a full and complete response to the Action. In conclusion, Applicants submit that, in light of the foregoing remarks, the present case is in condition for allowance, and such favorable action is respectfully requested. Should Examiner Steadman have any questions or comments, or believe that certain amendments of the claims might serve to improve their clarity, a telephone call to the undersigned Applicants' representative is earnestly solicited.

Respectfully submitted,

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